Bond University

Research Repository

Incompletely Reported Important Methodological Details and Inaccurate Description of the Formulation That the Control Arms Received in a Gardasil Vaccine Trial

Bourgeois, Florence; Doshi, Peter; Hong, Kyungwan; Jefferson, Tom; Jones, Mark; Lee, Haeyoung; Rowhani-Farid, Anisa; Shamseer, Larissa; Spence, O'Mareen M.

Published in:
mSphere

DOI:
10.1128/mSphere.00770-20

Licence:
CC BY

Link to output in Bond University research repository.

Recommended citation(APA):
Bourgeois, F., Doshi, P., Hong, K., Jefferson, T., Jones, M., Lee, H., Rowhani-Farid, A., Shamseer, L., & Spence, OM. M. (2020). Incompletely Reported Important Methodological Details and Inaccurate Description of the Formulation That the Control Arms Received in a Gardasil Vaccine Trial. *mSphere*, *5*(6), 1-3. https://doi.org/10.1128/mSphere.00770-20

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

For more information, or if you believe that this document breaches copyright, please contact the Bond University research repository coordinator.

Download date: 06 May 2023

LETTER TO THE EDITOR
Clinical Science and Epidemiology

Incompletely Reported Important Methodological Details and Inaccurate Description of the Formulation That the Control Arms Received in a Gardasil Vaccine Trial

Florence Bourgeois,[a] Peter Doshi,[b] Kyungwan Hong,[b] Tom Jefferson,[c,d] Mark Jones,[e] Haeyoung Lee,[b] Anisa Rowhani-Farid,[b] Larissa Shamseer,[f] O'Mareen Spence[b]

[a]Department of Pediatrics, Harvard Medical School, Boston, Massachusetts, USA
[b]Department of Pharmaceutical Health Services Research, University of Maryland School of Pharmacy, Baltimore, Maryland, USA
[c]Centre for Evidence-Based Medicine, University of Oxford, Oxford, United Kingdom
[d]Nordic Cochrane Centre, Copenhagen, Denmark
[e]Institute for Evidence-based Healthcare, Bond University, Gold Coast, Queensland, Australia
[f]University of Ottawa, Ottawa, Ontario, Canada

KEYWORDS drug regulation, drug safety, evidence-based medicine, transparency

The Restoring Invisible and Abandoned Trials (RIAT) initiative is an international effort concerned with two fundamental problems in the scientific literature on clinical trials: many trials are inaccurately or incompletely reported in journal publications and not all trials conducted are even published. RIAT aims to address these problems by offering a methodology that allows other people to responsibly correct the record (1).

We are writing with concerns about inaccurate and incomplete reporting in a trial published in *Clinical and Vaccine Immunology*, as well as ethical concerns about the informed consent process.

In their study of quadrivalent human papillomavirus vaccine (NCT00092482) (2), the authors stated that they conducted a "placebo-controlled" trial. However, control arm participants did not receive a "placebo" or an "inactive solution," the descriptions provided in the informed consent forms for this trial. Instead, they received an injection containing amorphous aluminum hydroxyphosphate sulfate (AAHS), a proprietary adjuvant added to enhance immune response (3). The use of the term "placebo" to describe an active and reactogenic comparator like AAHS inaccurately describes the formulation that the control arm received and may also have obscured an accurate assessment of vaccine safety. Further, the publication does not report the rationale for the selection of AAHS control, an important omission that constitutes underreporting of important methodological details.

According to the manufacturer's clinical study report for this trial, the rationale for selecting AAHS adjuvant as the control was as follows:

> "Aluminum adjuvant was chosen as the appropriate control for the qHPV vaccine for the following reasons:
>
> The inclusion of aluminum adjuvant in both vaccine and placebo preserved the blinding of the study because it allowed the vaccine and placebo to be visually indistinguishable; and
>
> The safety profile of Merck's aluminum adjuvant is well characterised. On the other hand, the safety profile of the HPV 6, 11, 16 and 18 L1 VLPs required further evaluation in humans. By using placebo that contained a dose of aluminum adjuvant that was identical to the dose included in the qHPV vaccine, it was possible to assess the safety profile attributable to the HPV 6, 11, 16 and 18 L1 VLP component of the vaccine" (3).

Citation Bourgeois F, Doshi P, Hong K, Jefferson T, Jones M, Lee H, Rowhani-Farid A, Shamseer L, Spence O. 2020. Incompletely reported important methodological details and inaccurate description of the formulation that the control arms received in a Gardasil vaccine trial. mSphere 5:e00770-20. https://doi.org/10.1128/mSphere.00770-20.

Editor Michael J. Imperiale, University of Michigan-Ann Arbor

Copyright © 2020 Bourgeois et al. This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International license.

Address correspondence to Peter Doshi, pdoshi@rx.umaryland.edu.

For the author reply, see https://doi.org/10.1128/mSphere.01010-20.

Published 4 November 2020

Downloaded from http://msphere.asm.org/ on February 24, 2021 by guest

Thus, the manufacturer's stated rationale for selecting AAHS as a control (to characterize the safety of human papillomavirus [HPV]-like particles) lacks clinical relevance, and a nonplacebo control may have obscured an accurate assessment of quadrivalent HPV vaccine safety (3). We have documented all of these issues elsewhere (3).

ACKNOWLEDGMENTS

Florence Bourgeois' work is supported by a grant from the Burroughs Wellcome Fund and by the Harvard-MIT Center for Regulatory Science. The Laura and John Arnold Foundation funds the RIAT Support Center, which supports the salaries of Peter Doshi (P.D.), Kyungwan Hong (K.H.), Mark Jones (M.J.), Tom Jefferson (T.J.), and Anisa Rowhani-Farid (A.R.-F.). In addition, P.D. has received travel funds from the European Respiratory Society (2012) and Uppsala Monitoring Center (2018) and grants from the Laura and John Arnold Foundation (2017–21), American Association of Colleges of Pharmacy (2015), Patient-Centered Outcomes Research Institute (2014–16), Cochrane Methods Innovations Fund (2016–18), and UK National Institute for Health Research (2011–14) and is an editor at The BMJ and unpaid member of the Reagan-Udall Foundation for the FDA. K.H. received the Maryland CERSI Scholar award from the Food and Drug Administration (grant 5U01FD005946-04). M.J. reports research funds from the Cochrane Methods Innovation Fund to assist with providing interim guidance on the inclusion of clinical study reports and other regulatory documents in Cochrane Reviews. He is also deputy coordinating editor for the Cochrane Acute Respiratory Infections Group. T.J. was in receipt of a Cochrane Methods Innovations Fund grant to develop guidance on the use of regulatory data in Cochrane Reviews (2015–2018). In 2014 to 2016, T.J. was a member of three advisory boards for Boehringer Ingelheim. T.J. is occasionally interviewed by market research companies about phase I or II pharmaceutical products for which he receives fees (current). T.J. was a member of an independent data monitoring committee for a Sanofi Pasteur clinical trial on an influenza vaccine (2015–2017). T.J. is a relator in a False Claims Act lawsuit on behalf of the United States that involves sales of Tamiflu for pandemic stockpiling. If resolved in the United States' favor, he would be entitled to a percentage of the recovery. T.J. is coholder of a Laura and John Arnold Foundation grant for development of a RIAT support center (2017–2020) and Jean Monnet Network Grant, 2017–2020, for The Jean Monnet Health Law and Policy Network. T.J. is an unpaid collaborator to the project Beyond Transparency in Pharmaceutical Research and Regulation led by Dalhousie University and funded by the Canadian Institutes of Health Research (2018–2022). T.J. consulted for Illumina LLC on next-generation gene sequencing (2019–2020). T.J. was the consultant scientific coordinator for the HTA Medical Technology program of the Agenzia per i Serivizi Sanitari Nazionali (AGENAS) of the Italian MoH (2007–2019). T.J. is Director Medical Affairs for BC Solutions, a market access company for medical devices in Europe. T.J. is funded by NIHR UK and the World Health Organization (WHO) to update Cochrane review A122, "Physical interventions to interrupt the spread of respiratory viruses." T.J. is funded by Oxford University to carry out a living review on the transmission epidemiology of COVID-19. Since 2020, T.J. has received fees for articles published by *The Spectator* and other media outlets. A.R.-F., Haeyoung Lee, and Larissa Shamseer have no competing interests to declare. O'Mareen Spence has received the Maryland CERSI Scholar award from the Food and Drug Administration (grant 1U01FD005946) and the PhRMA Foundation's Predoctoral Fellowship in Health Outcomes. This project was supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award (U01FD005946) totaling $5,000 with 100% funded by FDA/HHS. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement by, FDA/HHS or the U.S. government.

Downloaded from http://msphere.asm.org/ on February 24, 2021 by guest

REFERENCES

1. Doshi P. 2020. Restoring Invisible & Abandoned Trials Support Center. https://restoringtrials.org/. Accessed 3 June 2020.
2. Garland SM, Steben M, Hernandez-Avila M, Koutsky LA, Wheeler CM, Perez G, Harper DM, Leodolter S, Tang GWK, Ferris DG, Esser MT, Vuocolo SC, Nelson M, Railkar R, Sattler C, Barr E, 012 Study Investigators. 2007. Noninferiority of antibody response to human papillomavirus type 16 in subjects vaccinated with monovalent and quadrivalent L1 virus-like particle vaccines. Clin Vaccine Immunol 14:792–795. https://doi.org/10.1128/CVI.00478-06.
3. Doshi P, Bourgeois F, Hong K, Jones M, Lee H, Shamseer L, Spence O, Jefferson T. 2020. Adjuvant-containing control arms in pivotal quadrivalent human papillomavirus vaccine trials: restoration of previously unpublished methodology. BMJ Evid Based Med https://doi.org/10.1136/bmjebm-2019-111331.

Downloaded from http://msphere.asm.org/ on February 24, 2021 by guest